

Performance of research ethics committees in Spain. A prospective study of 100 applications for clinical trial protocols on medicines

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Abstract

Objectives—To review the characteristics and performance of research ethics committees in Spain in the evaluation of multicentre clinical trial drug protocols.

Design—A prospective study of 100 applications.

Setting—Forty-one committees reviewing clinical trial protocols, involving 50 hospitals in 25 cities.

Main measures—Protocol-related features, characteristics of research ethics committees and evaluation dynamics.

Results—The 100 applications involved 15 protocols (of which 12 were multinational) with 12 drugs. Committees met monthly (except one). They had a mean number of 12 members, requested a mean of six complete dossiers and nine additional copies of the protocol with a mean deadline of 14 days before the meeting. All applications were approved except three (two of the three were open-label long-term safety trials rejected by the same committee), which were approved by the other committees involved. The mean time from submission to approval was 64 days. The mean time from submission to arrival of the approval document at our offices was 85 days. Twenty-five committees raised queries for 38 of the 97 finally approved applications. Impact of evaluation fee, number of members, queries raised and experience of committees on timings were not statistically significant.

Conclusion—Obtaining ethical approval is time-consuming. There is much diversity in the research ethics committees' performance. A remarkable delay (> 20 days) exists between the decision and the arrival of the written approval, suggesting administrative or organisational problems.

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research ethics committees (RECs) is a compulsory step for any clinical research trial. Since 1982, the Spanish regulation states that, before starting a clinical trial, the protocol must be approved by all RECs of all participating centres. The regulation changed in the 1990s¹ and included significant modifications such as the inclusion of lay members in the RECs and the full implementation of good clinical practice guidelines. The complete dossier to be submitted to the RECs includes: protocol (according to a 12-item format); case report form; investigator's brochure; patient information sheet; consent form (in an official format), and also a number of appendices, including a health insurance coverage. The REC's approval (official form) must be sent to the sponsor who must submit it (with the complete dossier) to the Ministry of Health for approval.

Some years ago, the pharmaceutical industry started a review of the processes involved in developing new drugs with the aim of reducing the time required to market a medicinal product. The standards for the conduct of clinical trials have been progressively developed on a worldwide basis, the International Conference on Harmonisation being the most important forum for debate and agreement between health authorities and the pharmaceutical industry in the US, Japan and the European Union. In addition, most research-based companies are assessing the variety of processes involved, from the inception of a clinical development plan through to its completion. One of these assessments focuses on the start-up of trials at the study centres. As part of such an assessment the time needed for obtaining RECs' approval should be considered, since this impacts on the start of all trials. In the current decade a number of reports about the performance of RECs in this respect have been published, particularly on the issues regarding multicentre studies in the UK²⁻¹³ and elsewhere.¹⁴ Recent data show that Spain is increasingly involved in multinational

Following the Declaration of Helsinki and international regulations, review of a study protocol by

trials.¹⁵ Some information is available on the time required by RECs in Spain for reviewing and approving clinical trial protocols, but this was obtained in 1992-93, before the current regulation was approved.¹⁶ We now report the results obtained from 100 applications to RECs for multicentre drug studies sponsored by our company in Spain which were submitted after the above mentioned regulatory change.

Material and methods

The RECs' review process of the first 100 applications for multicentre drug trial protocols submitted by our department in Spain since January 1995 has been evaluated. A specific 40-item database was prospectively designed. Items were divided into four categories: a) identification of product, protocol and therapeutic area; b) type of clinical trial: phase II-IV, number of centres, design features (parallel-group, placebo or active control, blinding, etc); c) characteristics of the REC (number of members, frequency of meetings, documents requested and deadline for submission of these before the REC's meeting, advanced evaluation fee, etc), and d) review and approval dynamics, which included not only days between submission of documentation and the answer from the REC but whether queries were raised or not, as well as their type and the REC's final decision (approval or rejection). The term "query" refers to questions asked of the investigator/sponsor about any part of the submitted documentation (protocol and/or appendices). When those queries resulted in the request for a change in the contents of the protocol and/or appendices this was recorded on the database. The documentation to be submitted to the RECs consisted of several copies of the complete dossiers and the protocol alone, without additional documentation.

Descriptive statistics values are presented. The potential impact of several factors on timings was assessed: evaluation fee; number of members of the RECs; a large v a low number of applications evaluated, and whether queries were raised or not. All comparisons were made by a one-way analysis of variance (SPSS programme, version 6.1 for Windows). Values are expressed as mean (SD), median and range.

Results

The 100 applications evaluated involved 12 drugs in 15 protocols (three phase II, ten phase III and two phase IV), 12 of them being multinational trials. The design features included 13 controlled (ten with placebo, ten double-blind) and two

open-label follow-up studies, involving the following therapeutic areas: anti-infectives; cardiovascular; endocrinology; neurology; oncology; psychiatry; rheumatology, and urology. The applications involved trials to be conducted in 41 teaching hospitals, eight primary care centres, four sexually transmitted diseases clinics and one dementia outpatient clinic in 25 cities from 12 regions. They were evaluated by a total of 41 different RECs, 18 of them located in the Madrid and Catalonia regions. Regarding the size of hospital, 17 have > 1,000 beds, 18 have 500-1,000 beds and six have 150-500 beds.

Research ethics committees met monthly in all cases except one, which had a meeting every two weeks. They consisted of a mean of 12 members (range 7-23, median 13). Research ethics committees requested a mean of six copies of the complete dossier (range 1-16, median four) and nine of the protocol alone (range 2-23, median ten). In all but three cases (which made no specific demands as to a deadline before the meeting), submission deadline was 14 days (mean) before the RECs' meeting (range 10-30, median 15). Mean (SD) time from submission to arrival of RECs' decision form for all 100 applications was 87 (54) days (median 70, range 23-238 days).

Only three out of the 100 applications were rejected by the RECs. Two of them, rejected by the same REC, were open-label follow-up extension studies for multinational trials of different therapeutic areas, aiming at the collection of long term safety data for regulatory purposes. The argument behind these decisions was that a long term safety evaluation without knowing the results of the original trial was not acceptable. Both protocols had been previously approved by the remaining Spanish RECs involved (13 and three respectively) as well as by other RECs of other European and North American centres participating in these studies. The third protocol, a double-blind, parallel-group, placebo-controlled study in double depression, was rejected because the REC considered the conduct of the study by primary care psychiatrists unacceptable. This local study was approved by two other RECs.

For the 97 approved applications, mean time from submission to arrival of RECs' approval at our offices was 85 days. No statistically significant differences were observed when variables such as request for an evaluation fee (ranging from £200 to £560) or number of members (larger or smaller than the median value) were considered (table 1). However, the difference observed (21 days) when the latter was taken into account seems relevant.

Four RECs evaluated 25 of the 97 approved applications. Timings of the review process for

Table 1 *Time (days) from submission to arrival of research ethics committees' (RECs) approval of 97 applications: results for full sample and by characteristics of RECs*

	<i>Submission-approval mean (SD), median, range</i>	<i>Approval-arrival mean (SD), median, range</i>	<i>Submission-arrival mean (SD), median, range</i>
Full sample (n=41)	64 (51), 46, 1-231	21 (20), 14, 1-104	85 (53), 69, 23-238
Evaluation fee			
Yes (n=14)	57 (43), 42, 18-199	24 (26), 14, 1-104	81 (51), 67, 24-199
No (n=27)	69 (55), 50.5, 1-231	18 (16), 13.5, 1-73	87 (55), 72.5, 23-238
No of members			
≥ 13 (n=21)	60 (47), 46, 10-229	16 (14), 12, 1-65	76 (49), 60, 24-236
< 13 (n=20)	72 (57), 51, 1-231	25 (25), 15.5, 1-104	97 (56), 82, 23-238

n = number of RECs with a given characteristic.

Table 2 *Time (days) from submission to arrival at sponsor's office of research ethics committees' (RECs) approval of 97 applications: 4 RECs which assessed 26% of applications v 37 which assessed 74% of applications*

	<i>Submission-approval mean (SD), median, range</i>	<i>Approval-arrival mean (SD), median, range</i>	<i>Submission-arrival mean (SD), median, range</i>
4 RECs (n=25)	52 (37), 41, 18-163	16 (11), 14, 2-43	68 (39), 54, 24-173
37 RECs (n=72)	69 (55), 47.5, 1-231	21 (23), 14, 1-104	90 (56), 71.5, 23-238

n = number of applications assessed.

Table 3 *Impact of queries raised by research ethics committees (RECs) on time (days) needed from submission to arrival at sponsor's office of RECs' approval of 97 applications*

	<i>Submission-approval mean (SD), median, range</i>	<i>Approval-arrival mean (SD), median, range</i>	<i>Submission-arrival mean (SD), median, range</i>
Applications with queries raised n=38 (No of RECs: 25)	78 (61), 50, 10-229	17 (21), 10, 1-104	95 (61), 75, 24-236
Applications without queries n=59 (No of RECs: 16)	56 (42), 42, 1-231	22 (20), 15, 1-102	78 (46), 69, 23-238

these RECs compared to the remaining ones are shown in table 2. Again, no statistically significant differences were observed, but a difference of more than three weeks is remarkable.

Twenty-five RECs raised queries in 38 out of 97 approved applications, involving 12 of the 15 protocols. Fifty-two per cent of the queries referred to protocol-related issues (design features, selection criteria, study procedures, statistics, case report form, etc), and 38% to ethical aspects (most commonly to the wording of the patient's information sheet and less frequently to the insurance coverage). Only six queries resulted in changes being made to the protocol (one referred to more clear wording of a selection criterion) or appendices (four referred to the wording of informed consent and one referred to the sign-off of the consent form). All queries were answered within three days. Though shorter submission-arrival timings were observed for applications in which no queries were raised, the difference (17 days) was not statistically significant (table 3). Figure 1 shows the time needed from submission to arrival of the RECs' approval form; 67% of these were received at our offices within 90 days.

Of particular interest is the analysis of the queries raised for two protocols in two areas of intensive clinical research. One was a six-month, dose-

ranging, double-blind, randomised, placebo-controlled phase II study for the evaluation of an investigational compound in Alzheimer's disease. The study was to be conducted in four countries, with 17 RECs reviewing the protocol in Spain. Twelve out of the 17 RECs raised 24 queries (table 4), nine of which were answered without providing additional information (ie merely by explaining further the information already submitted). The same query was raised by three RECs: each of the three pointed out the need to include the availability of alternative medication in the patient information sheet, since between the time when the protocol was submitted and its evaluation, tacrine was marketed in Spain.

The second trial was a large phase III study to evaluate the effects of a drug, (v placebo) added to standard therapy, on mortality in patients with left ventricular dysfunction in the acute phase of myocardial infarction. This trial was designed and directed by a steering committee composed of well-known international cardiology experts, independent of the sponsor, with a data safety monitoring board which was also independent of the sponsor. It was planned that ten countries would participate in this trial. In Spain, 15 RECs evaluated the protocol. Nine of these raised 22 queries (table 4), of which 13 were answered

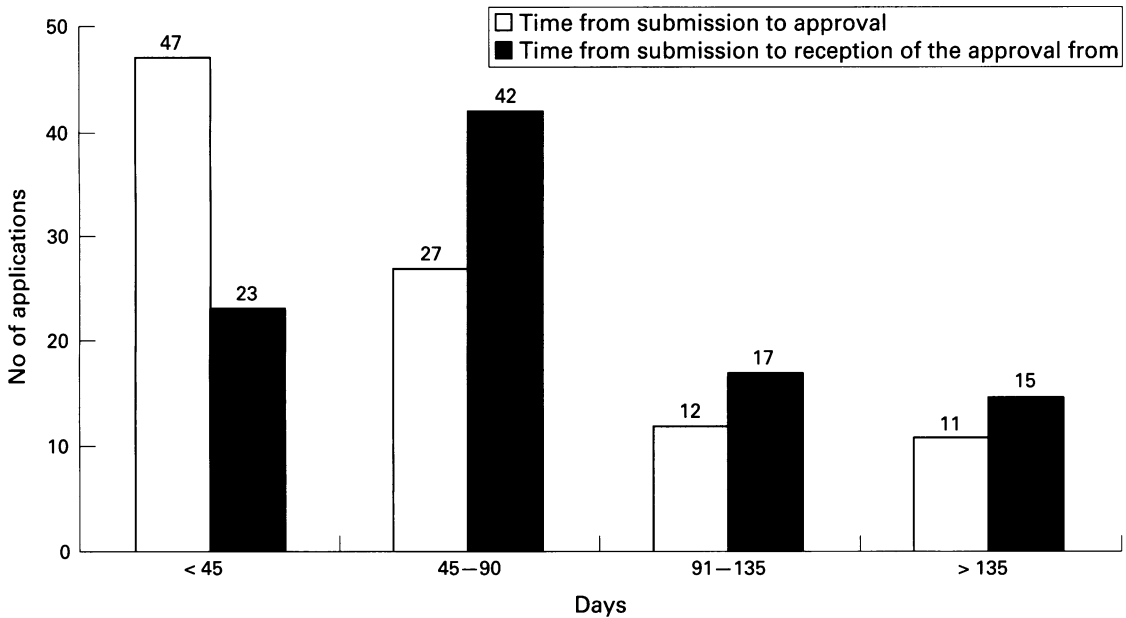


Figure 1. Approved applications ($n=97$): Time (days) from submission to research ethics committees' approval and from submission to arrival of the approval form at the sponsor's office.

Table 4 Type and number (n) of queries raised by research ethics committees on a phase II (Alzheimer's Disease) and phase III (Post Myocardial Infarction) trials

Type of queries	Phase II (n)	Phase III (n)
Protocol-related issues		
Study design	—	3
Selection criteria	3	—
Study procedures	1	5
Statistics	2	1
Other	1	1
Informed Consent		
Wording (a)	5	3
Consent form sign-off	3	1
Insurance cover	1	3
Medication	5	—
Others	3	5
Total	24	22

(a) Wording of the patient's information sheet.

without providing additional information. Only one query was common to two RECs.

Discussion

In the last two decades the time required by RECs to review protocols for research involving human subjects has been one of the problems faced by investigators. This is particularly relevant for multicentre studies, where a wide variation in performance and practice between RECs has been extensively reported in countries such as the UK.²⁻¹³ In the UK, until recently,¹⁷ all aspects of a given protocol needed approval by all RECs of all participating centres.

Two factors suggest that the sample of 41 RECs involved in this study is an accurate representation

of all Spanish RECs: a) these 41 RECs are located in those regions in which 95% of all clinical trials are performed,¹⁵ and b) those RECs located in the Madrid and Catalonia regions reviewed 49% of all applications included in this study. This is close to the figure of the 52% of all trials in our country which are conducted in these two regions.¹⁵

This study shows that the mean time between submission and approval for a given protocol is 64 days. However, as the REC's approval form must be submitted by the sponsor to the Ministry of Health, the critical time to consider is that between submission and arrival of the REC's approval at the sponsor's office. The mean time for this was 85 days, which is similar to that reported in the previous study (89 days)¹⁶ and in some others from the UK,^{5 9 13 18 19} but lower than the 109 days reported by Redshaw *et al.*¹² A delay > 20 days between approval and arrival of the approval form seems rather long. This may be due, as suggested by others,^{5 9 12 20} to lack of adequate competence in administrative matters or organisational problems of the RECs. It has been suggested²⁰ that having an administrator devoted to the bureaucratic activities of the REC would result in a greater efficiency of the committee in terms of dealing with paperwork. This, however, seems not to be the case in our country, since it appears reasonable to expect that those RECs asking for an evaluation fee had more extensive resources, resulting in a quicker review process. However, this was not the case either in this study or in the previous one.¹⁶

Three different factors have been assessed in this study with regard to their relevance on RECs' performance: a) RECs' experience, b) number of RECs' members, and c) queries raised by RECs about the protocols submitted. The Ministry of Health data show that the four RECs which reviewed 26% of applications in this study are among the eight busiest RECs in Spain.¹⁵ The review process of these RECs seemed to be somewhat quicker (68 days v 90 days). The same applies to larger (≥ 13 members) RECs, which required some 21 days less (nine of those in the approval-arrival stage) for the protocol review than smaller ones. Though no statistically significant differences could be found for the impact of these factors on the timings, there seems to be some trend towards shorter timings for larger and more experienced committees. This may be the result of better internal organisation and processes.

Sixty one per cent of applications were approved without queries being raised to the investigator/sponsor, similar to results shown in the 1992-93 study.¹⁶ On discussing queries, it is worth reviewing those raised in the two trials which have been specifically addressed in this study, where 21 out of 32 RECs raised 46 queries. As other authors have reported^{6 9 10 12} a wide range of queries were raised. Irrespective of who designed the protocol (company experts or external international experts) protocol-related topics were the commonest source of queries ($n=17$). Both trials were eventually approved by all RECs without changes. With this in mind, why did not all RECs approve these protocols provided they received satisfactory answers to the questions raised, without waiting for a further formal REC meeting? This approach is in place in a number of RECs.

The most important factor in the quality of a REC's work is the attitude and commitment of its members.^{21 22} Although some diversity among RECs should be expected, due to the subjective nature of ethical considerations and local needs,^{3 4 23} the large variations in practice among different RECs may be a deterrent to research.^{6 24} These variations can have important implications, namely, the time and expense involved in the submission process for the investigators; the subsequent delay or rescheduling of the start of the study, and the disincentive to useful research that may result.²⁵ In addition, money for research is becoming very scarce, and researchers have no confidence that another grant will be forthcoming if the current one is delayed.²¹

This study shows that, as in the UK, there is room for improvement in the overall performance of RECs in Spain. This is relevant when consider-

ing that the most recent data published by the Ministry of Health show that the number of multicentre multinational trials has increased to up to 70% of all drug trials performed in Spain.¹⁵ Various suggestions can be made as to how the efficiency of RECs might be improved. For instance, if the complete dossier of a clinical trial must be submitted to all RECs 10-30 days before the review meeting, and no queries are raised, it seems reasonable that the approval form should be received by the sponsor within a 25-45-day period. In this study less than 25% of the applications would have met this criterion. To speed up this process RECs should consider, as suggested by Alberti,¹¹ the use of electronic transmission or fax to inform the sponsor immediately of the decision. If it seems evident that RECs should have adequate manpower to deal with the paperwork, then this should be even more apparently so for those RECs asking for a fee, and this should translate into much greater efficiency, ie reduction of time between submission and arrival of approval. Regarding this aspect, an increasing number of hospitals are creating specific units to deal with the organisation of trials in their centres; these units are the link between investigators, sponsors, REC and hospital administration, and they have proved to be an efficient tool to accelerate the process of starting a clinical trial.

Most clinical trials are sponsored by industry²⁶; this is especially true in Spain where 90% of trials are sponsored by pharmaceutical companies.²⁷ In the 1990s clinical research has increased significantly in our country. To maintain, or even increase, the number of trials conducted in Spain, the more than 100 RECs²⁷ already in place should realise that the time needed to assess and approve clinical trial protocols is one of the factors which is being carefully considered by research-based companies, when they are deciding in which countries a study should take place. The delay in the initiation of clinical trials is an issue in Spain and the UK, and in other European countries as well, and affects not only industry-sponsored trials but also those sponsored by international groups and organisations. The European Commission has acknowledged that this delay has a negative impact on research in Europe,²⁸ and is working on a clinical trials directive which aims, among other things, to harmonise and streamline the study-start process within the European Union.

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References

- Real Decreto 561/1993, de 16 de Abril. BOE, 13 de Mayo de 1993.
- Ashford JJ. Recent experience of ethics committee review of a multicentre research project. *British Journal of Clinical Pharmacology* 1987;23:373-4.
- Gilbert C, Fulford KWM, Parker C. Diversity in the practice of district ethics committees. *British Medical Journal* 1989;299:1437-9.
- Lock S. Monitoring research ethics committees. *British Medical Journal* 1990;300: 60-1.
- Watling MIL, Dewhurst JK. Current experience of central versus local ethics approval in multicentre studies. *Journal of the Royal College of Physicians of London* 1993;27:399-402.
- Harries UA, Fentem PH, Tuxworth W, Hoinville GW. Local research ethics committees. Widely differing responses to a national survey protocol. *Journal of the Royal College of Physicians of London* 1994;28:150-4.
- Garfield P. Cross district comparison of applications to research ethics committees. *British Medical Journal* 1995;311: 660-1.
- While AE. Ethics committees: impediments to research or guardians of ethical standards?. *British Medical Journal* 1995;311:661, 792.
- Penn ZJ, Steer PJ. Local research ethics committees: hindrance or help? *British Journal of Obstetrics and Gynaecology* 1995;102: 1-2.
- Hotopf M, Wessely S, Noah N. Are ethics committees reliable? *Journal of the Royal Society of Medicine* 1995;88:31-3.
- Alberti KGMM. Local research ethics committees. *British Medical Journal* 1995;311:639-40.
- Redshaw ME, Harris A, Baum JD. Research ethics committee audit: differences between committees. *Journal of Medical Ethics* 1996;22:78-82.
- Ahmed AEH, Nicholson KG. Delays and diversity in the practice of local research ethics committees. *Journal of Medical Ethics* 1996;22:263-6.
- Barth H, Hopkins G, Groves R. Good clinical practice and ethics in European drug research: a case study from the pharmaceutical industry. In: Bennet P, ed. *Good clinical practice and ethics in European drug research*. Bath: Bath University Press, 1994: 49-66.
- Diego P, Cuaresma E, Tristán C, Chaparro P. *Ensayos clínicos en España (1993-1995)*. Monografías Técnicas, N° 21. Madrid: Ministerio de Sanidad y Consumo, 1996.
- Ortega R, Dal-Ré R. Clinical trials committees: how long is the protocol review and approval process in Spain? A prospective study. *IRB A Review of Human Subjects Research* 1995;17,4:6-9.
- Department of Health. *Ethics committee review of multicentre research*. London: Department of Health, 1997. HSG (97) 23.
- Benster R, Pollock A. Ethics and multicentre research projects. *British Medical Journal* 1992;304:1696.
- Ginzler M, Davies J, McPherson K, Black N. Ethics committees and health services. *Journal of Public Health Medicine* 1990;12:190-6.
- Neuberger J. Too many ethics committees. *British Medical Journal* 1991;302:180.
- Edgar H, Rothman DJ. The institutional review board and beyond: future challenges to the ethics of human experimentation. *The Milbank Quarterly* 1995;73:489-506.
- Dudley H. Local research ethics committees. Attitudes of their members is the critical factor. *British Medical Journal* 1995;311:1571.
- Madden AP. Research ethics committees. *British Medical Journal* 1990;300:607-8.
- Crooks SW, Colman SB, Campbell IA. Costs and getting ethical approval deter doctors from participating in multicentre trials. *British Medical Journal* 1996;312:1669.
- Meade TW. The trouble with ethics committees. *Journal of the Royal College of Physicians of London* 1994;28:102-4.
- Friedman L. Financing of clinical trials. In: Fracchia GN, Haavisto KH, eds. *European medicines research. Perspectives in clinical trials*. Cambridge: European Conference Publications, 1996: 89-93.
- Dal-Ré R. Comités éticos de investigación clínica: algo más que el cambio de nombre. *Medicina Clínica (Barcelona)* 1995;105: 580-2.
- Donnelly MC. Future European regulatory trends. See reference 26: 53-62.